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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,630	11/28/2001	Kimberly A. Gillis	102729-10 (AM 100491)	3476

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,630	GILLIS ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *23-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 51-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action and amendment filed on December 1 2004, has been entered and considered.

2. New claims 51-54 are added. Claims 1-54 are pending. Claims 23-50 are withdrawn as being non-elected claims. Claims 1-22, 51-54 are considered for examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 51-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims".

The nature of the invention:

The instant claims (claim 1 and 17) are drawn to a method for assessing whether a subject is afflicted with prostrate cancer, comprising comparing (a) the level of expression of KIAA marker(s) KIAA 18 and KIAA 96 in a sample from a subject, with (b) the normal level of expression of the marker in a control sample, wherein a significant difference in the level of expression of the marker in the sample and in the normal level of expression of the marker in a control, is an indication that the subject is afflicted with prostrate cancer. The dependent claims further limitations, limiting the instant claim 1, drawn to said marker as a transcribed polynucleotide (mRNA, cDNA), said sample comprises cells from a prostate gland of a subject, level of expression said marker in a subject afflicted with prostate cancer and a control, detection of the level of expression in assessing whether a subject is afflicted with prostate cancer.

The amount of direction or guidance presented:

The specification discloses KIAA clones (KIAA 18 and KIAA 96) as genetic markers for this detection, diagnosis and prognosis of prostate disorders. The specification also disclose a number of other KIAA clones that encode enzymes kinases, as genetic markers for detection, diagnosis and prognosis of prostate disorders. The specification on page 10 discloses that the expression of these markers is increased (KIAA) or decreased in androgen dependent prostate cancer cells. However, the specification has not established any defined measure of statistically significant level of expression of any particular KIAA marker or a threshold level of expression beyond which a subject could be assessed as having prostate cancer. The specification fails to establish any correlation between the level of expression of KIAA markers and the prostate cancer in general because the specification discloses the expression of KIAA markers is androgen dependent and does not provide any information regarding the expression level for

other types of prostrate cancers. Further the specification provides the relative measure of the level of expression as increase or decrease relative to control samples by at least 2-, 3-,.....10-fold or more. Thus the specification fails to establish a defined level of expression threshold, which could be correlated to the development of prostate cancer in general, especially because the specification relays on the KIAA 18 and KIAA 96, of which the expression of KIAA 18 increase and the level of KIAA 96 decreases relative to control samples.

Presence and absence of working examples:

The specification discloses in vitro identification of a marker cDNA, by screening about 6000 full-length human genes on a chip, in response to natural androgen in LNCaP cells. The genes that showed statistically significant for treatment and interaction were considered. Further the role of KIAA (KIAA18 or KIAA 96) in solid tumors, tissue microarray analysis was performed and the gene expression using self-organizing maps were considered for classifying the expression data in response to androgen treatment. Based on the results, the specification concludes that KIAA 18 is up-regulated and KIAA 96 is down-regulated in LNCap cancer cells upon androgen treatment. The specification also discloses the differential expression of KIAA 18 and KIAA 96 in different grades of solid tumors.

The specification relays on in vitro data on the level of expression of KIAA 18 and KIAA 96. The specification does not provide any experimental data on the expression levels of KIAA 18 or KIAA 96, using samples from subjects with and without prostate cancer to assess whether a subject is afflicted with any specific prostate cancer or prostate cancer in general. The specification has not established any statistically significant association between the level of expression of these markers in subjects with and without any specific prostate cancer.

Level of predictability in the art:

Predictability in the art identified a number of KIAA clones. Nagase et al. identified about 40 new KIAA genes and suggest that KIAA 0096, 0099, and 00118 were related to signal transducing genes on the basis of sequence similarities and characteristic protein motifs. Particularly, it was noted that KIAA0096 gene carries sequences with similarities to the genes in the protein kinase family (Nagase et al. DNA Res., Vol. 2, pages 37-43, 1995). An et al. disclose methods for the detection of metastatic prostate cancer by correlating the quantity of expression of a metastatic prostate cancer marker gene selected from prostate-specific transglutaminase, cytokeratin 15, or semenogelin II (US 5, 872,615). However, the art did not establish any predictable association of any of the KIAA gene markers or any other gene markers with any specific prostate cancer or the prostate cancer in general. It is apparent from the prior art that the unpredictability is high in assessing whether a subject is afflicted with any specific prostate cancer or prostate cancer in general by correlating the level of expression of any KIAA genes in general or specific KIAA 18 or KIAA 96 gene markers. In addition to the unpredictability in the art, the instant specification fails to establish any association of particular level of expression of the specific KIAA 18 or KIAA 96 in a subject with or without any specific prostrate cancer or prostate cancer in general. Given the broad scope of the instant claims, the specification does not provide any specific example that would easily predict a significant association of the level of expression of KIAA 18 or KIAA 96 with any particular prostate cancer or prostate cancer in general.

Qunatity of experimentation necessary:

Given the lack of guidance in the specification and the unpredictability in the art, it would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that would associate the level of these KIAA markers with any particular prostate cancer or would provide a predictable measure in assessing whether a subject is afflicted with prostate cancer. To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different types of prostate cancer and matched control subjects to determine if any general measure of the expression of these KIAA markers was associated with any specific prostate cancer or prostate cancer in general for assessing whether a subject is afflicted with prostate cancer in general based of the level of expression of these markers.

Conclusion:

As discussed above, the level of unpredictability is high in the art, the specification provides no guidance that would provide a predictable measure of expression of these KIAA markers in assessing whether a subject is afflicted with prostate cancer in general, one skilled in the art cannot readily anticipate the effect of change within the subject matter to which the claimed invention pertains. Thus given the broad scope of the claims in an art whose nature is identified as unpredictable, the large quantity of research is required to define these unpredictable variables. The lack of guidance in the specification, the absence of any working examples, it would require undue experimentation for one skilled artisan to perform the method of the claimed invention as broadly written.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-22, 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over An et al. (USPN. 5, 972,615) in view of Nagase et al. (DNA Res., Vol. 2, pages 37-43, 1995).

An et al. teach a method of 18, for detecting metastatic prostate disease state in a subject, comprising

(a) detecting in a subject sample at a first point in time the expression of KIAA marker (prostrate specific-transglutaminase) (see column 4, lines 16-25);

(c) comparing the level of expression of step a with the level of expression in a control sample (see column 4, lines 25-35).

With regard to step (b) of the instant claim 18, An et al. also disclose that the levels of expression are measured in normal tissues or in tissue from subjects in other states (progression of disease states) of prostate disease (see column 4, lines 35-40, column 7, lines 24-34).

An et al. also teach that the sample comprises cells obtained from a subject (see column 4, lines 16-19); cells collected from prostate tissue (see column 4, lines 16-19); and cells collected from blood (see column 27, lines 1-8).

However, An et al. did not specifically teach expression of KIAA 18 (SEQ ID NO. 10) or KIAA 96(SEQ ID NO. 11).

Nagase et al. teach a method of screening about 40 KIAA markers which includes KIAA 096 and KIAA 0018,wherein Nagase et al. teach that KIAA096 gene carries sequences with similarities to the genes in protein kinase family and is related to signal transducing genes (see page 40, column 1, lines 9-16, see sequence alignment).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting the expression of KIAA markers as taught by An et al. with the teachings of KIAA 0018 and KIAA 96 as taught by Nagase et al. to achieve expected advantage of developing an improved method for monitoring the progression of prostate cancer in a subject disease because Nagase et al. taught the role of KIAA markers in signal transduction and similarities with protein kinase gene family (see page 40, column 1, lines 9-16). Thus an ordinary practitioner would have motivated to combine the method of detecting and monitoring the progression of prostate cancer in a subject as taught by An et al. with the addition of the step of specific KIAA markers involved in signal transduction pathway as taught by Nagase et al. which would result in developing an improved and sensitive method which would provide a better prognosis of prostate cancer.

Response to arguments

5. Applicants' response to the office action is fully considered and found persuasive in part.

6. With reference to the rejection maintained in the previous office action under 35 USC 112, second paragraph, applicants' arguments and amendment are fully considered and the rejection is withdrawn in view of the amendment.

7. With reference to the rejection as reiterated above under 35 USC 112 first paragraph, applicants' arguments and amendment are fully considered and found unpersuasive. Applicants' argue that LnCap cell line is useful as in vitro model for the study of regulation of prostate related genes since that expression of many prostate-specific proteins require functionally differentiated, androgen-responsive cells and argue that a skilled artisan could easily extrapolate the correlation between the LNCap cell line and prostate cancer. These arguments are fully considered and found unpersuasive. It is noted that these arguments are irrelevant to the present context, because the instant claims are not drawn to a correlation between LNCap cell line and Prostate cancer, rather the instant claims are drawn to a correlation between the regulation of specific KIAA markers and the assessment of whether a subject is afflicted with prostate cancer or not.

Applicants further argue that the specification provides working examples, wherein KIAA 18 (SEQ ID NO. 10) expression is increased and KIAA 96 (SEQ ID NO. 11) is decreased depending on the increase in the tumor grade and argue that the correlation should be accepted according to MPEP 2164.02. Applicants also provide a declaration of Dr. Steven Haney under 37CFR 1.132 , which discloses that one skilled in the art would recognize LNCap cell line model used as a model of human prostate cancer and therefore one would assume that the expression of KIAA 18 and KIAA 96 markers in the LNCap cell line model would have similar result in cancer tissue. Applicants' arguments and the declaration are fully reviewed and considered and

found unpersuasive. As discussed above, the instant claims are not drawn to a correlation between LNCap cell line and prostate cancer. Further the working examples as shown in the specification disclose KIAA 18 expression increased as the tumor grade increased while a KIAA96 expression decreased as the tumor grade increased. These working examples and the arguments are fully considered. However the claims do not require alteration of both the markers, because the claim recites marker is selected from the group consisting of SEQ ID No. 10 (KIAA 18) and SEQ ID No. 11 (KIAA 96), thus the claims are drawn to any one of the markers and do not recite that the method requires both the markers that is, an increase in KIAA18 as the tumor grade increases while a decrease in KIAA 96 as the tumor grade increases. Thus the limitation upon which the arguments are based, is not present in the instant claims. Additionally, the specification fails to establish a defined level of expression threshold, that is, a particular level of expression of the specific KIAA 18 or KIAA 96 in a subject with or without any specific prostrate cancer or prostate cancer in general, that would provide one skilled in the art to easily predict a significant association of the level of expression of KIAA 18 or KIAA 96 with progression of any particular prostate cancer or prostate cancer in general, especially because the specification relays on the KIAA 18 and KIAA 96, of which the expression of KIAA 18 increases while the level of KIAA 96 decreases relative to the increase in tumor grade. Therefore the rejection is maintained herein and rewritten as above to include new claim limitations.

8. With reference to the rejection made in the previous office action under 35 USC 103(a), applicants' arguments and amendment are fully considered and found not persuasive. Applicants amended the claims the specific SEQ ID Nos. 10 and 11. Applicants' argue that neither An et al.

nor Nagase et al. teach KIAA markers and there is no motivation to combine the teachings of An et al. with Nagase et al. Applicants' arguments are fully considered and found not persuasive. The specification discloses on page 2, the examples of KIAA clones which include KIAA clones that encode enzymes such as kinases (e.g. serine-threonine kinases and tyrosine kinases), phospatases, transglutainases, proteins such as chaperone proteins, growth factors, oncogenes, transcription factors, antibodies and hormones. Given the broad scope of the term KIAA marker, An et al. teaches regulation of transglutaminases (KIAA marker) and it would have been prima-facie obvious to one skilled in the art to modify the teachings of An et al. with the specific KIAA markers as taught by Nagase et al. to achieve the expected advantage of developing a method for monitoring the prostate cancer because An et al. explicitly teach the screening of KIAA markers. Therefore the rejection is maintained herein and rewritten to include new claims 53-54.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
2/1/05